[1] *Arafa MF, Alshaikh RA, Abdelquader MM, El Maghraby GM*. **Co-processing of Atorvastatin and Ezetimibe for Enhanced Dissolution Rate: In Vitro and In Vivo Correlation**. AAPS PharmSciTech 2021; 22:59.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33517486

ABSTRACT

Development of fixed dose combinations is growing and many of these drug combinations are being legally marketed. However, the development of these requires careful investigation of possible physicochemical changes during co-processing. This requires investigation of the effect of co-processing of drug combination in absence of excipients to maximize the chance of interaction (if any). Accordingly, the aim was to investigate the effect of co-processing of ezetimibe and atorvastatin on drugs dissolution rate. The objective was extended to in vitro in vivo correlation. Drugs were subjected to wet co-processing in presence of ethanol after being mixed at different ratios. The prepared formulations were characterized using FTIR spectroscopy, X-ray powder diffraction, differential scanning calorimetry, scanning electron microscopy, and in vitro dissolution testing. These investigations proved the possibility of eutectic system formation after drugs co-processing. This was reflected on drugs dissolution rate which was significantly enhanced at dose ratio and 2:1 atorvastatin:ezetimibe molar ratio compared to the corresponding pure drugs. In vivo antihyperlipidemic effects of the co-processed drugs were monitored in albino mice which were subjected to hyperlipidemia induction using poloxamer 407. The results showed significant enhancement in pharmacological activity as revealed from pronounced reduction in cholesterol level in mice administering the co-processed form of both drugs. Besides, histopathological examinations of the liver showed marked decrease in hepatic vacuolation. In conclusion, co-processing of atorvastatin with ezetimibe resulted in beneficial eutexia which hastened the dissolution rate and pharmacological effects of both drugs.Graphical abstract.

[2] *Liu Q, Xu J, Liao K, Tang N*. **Oral Bioavailability Improvement of Tailored Rosuvastatin Loaded Niosomal Nanocarriers to Manage Ischemic Heart Disease: Optimization, Ex Vivo and In Vivo Studies**. AAPS PharmSciTech 2021; 22:58.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33502651

ABSTRACT

Rosuvastatin is an efficient antihyperlipidemic agent; however, being a BCS class II molecule, it shows poor oral bioavailability of < 20%. The present study focused on the improvement of oral bioavailability of rosuvastatin using tailored niosomes. The niosomes were prepared by film hydration method and sonication using cholesterol and Span 40. The Box-Behnken design (BBD) was applied to optimize the size (98 nm) and the entrapment efficacy (77%) of the niosomes by selecting cholesterol at 122 mg, Span 40 at 0.52%, and hydration time at 29.88 min. The transmission electron microscopy image showed spherical shape niosomes with smooth surface without aggregation. The ex vivo intestinal permeability studies showed significant improvement in the rosuvastatin permeation (95.5% after 2 h) using niosomes in comparison to the rosuvastatin suspension (40.1% after 2 h). The in vivo pharmacokinetic parameters in the rat model confirmed the improvement in the oral bioavailability with optimized rosuvastatin loaded niosomes (relative bioavailability = 2.01) in comparison to the rosuvastatin suspension, due to high surface area of niosomes and its lymphatic uptake via

transcellular route. In conclusion, the optimized rosuvastatin loaded niosomes offers a promising approach to improve the oral bioavailability of rosuvastatin.

[3] *Tombling BJ, Lammi C, Lawrence N et al.* **Engineered EGF-A Peptides with Improved Affinity for Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)**. ACS chemical biology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33512150
ABSTRACT
The epidermal growth-factor-like domain A (EGF-A) of the low-density lipoprotein (LDL) receptor is a promising lead for therapeutic inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9). However, the clinical potential of EGF-A is limited by its suboptimal affinity for PCSK9. Here, we use phage display to identify EGF-A analogues with extended bioactive segments that have improved affinity for PCSK9. The most potent analogue, TEX-S2_03, demonstrated ~130-fold improved affinity over the parent domain and had a reduced calcium dependency for efficient PCSK9 binding. Thermodynamic binding analysis suggests the improved affinity of TEX-S2_03 is enthalpically driven, indicating favorable interactions are formed between the extended segment of TEX-S2_03 and the PCSK9 surface. The improved affinity of TEX-S2_03 resulted in increased activity in competition binding assays and more efficient restoration of LDL receptor levels with clearance of extracellular LDL cholesterol in functional cell assays. These results confirm that TEX-S2_03 is a promising therapeutic lead for treating hypercholesterolemia. Many EGF-like domains are involved in disease-related protein-protein interactions; therefore, our strategy for engineering EGF-like domains has the potential to be broadly implemented in EGF-based drug design.

[4] *Roan JN, Lin WH, Tsai MT et al.* **Rosuvastatin Failed to Improve Arteriovenous Fistula Patency for Hemodialysis in Diabetic Patients - A Randomized Clinical Trial**. Acta Cardiologica Sinica 2021; 37:18-29.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33488024
ABSTRACT
BACKGROUND: Very limited therapeutic strategies exist to prevent the primary failure of arteriovenous (AV) fistulas in patients with diabetes. OBJECTIVES: To investigate whether rosuvastatin could improve the primary patency of AV fistulas in diabetic patients with stage 5 chronic kidney disease (CKD). METHODS: This was a double-blind randomized clinical trial. From July 2012 to September 2018, patients aged between 18 and 65 years with type 2 diabetes and stage 5 CKD were randomized to receive placebo or rosuvastatin (5 mg/day) for 7 days prior to the creation of an AV fistula on the forearm until the 21(st) day after surgery. Patients were followed up for 180 days after the operation. The primary composite endpoint was the development of fistula immaturity or stenosis. The secondary endpoints were changes in inflammatory markers, oxidative stress, and occurrence of postoperative complications. RESULTS: A total of 60 patients were enrolled in the study. Rosuvastatin resulted in a 20% reduction in total cholesterol from postoperative day 0 to 28 ($p = .0006$). The overall rate of AV fistula failure (immaturity or stenosis) was 30%, with no significant difference between patients receiving rosuvastatin and those receiving the placebo (33.3% vs. 26.7%, $p = .5731$). Although not statistically significant, the administration of rosuvastatin might have increased the

incidence of postoperative complications (2.99 vs. 2.39 event rate per 1000 patient-days; odds ratio, 1.33; p = .5986). CONCLUSIONS: Rosuvastatin showed no significant beneficial effects on the primary patency of AV fistulas in diabetic patients with stage 5 CKD, but might have been associated with the risk of drug-related complications.

[5] *Posch-Pertl L, Michelitsch M, Wagner G et al.* **Cholesterol and glaucoma: a systematic review and meta-analysis**. Acta ophthalmologica 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33506616
ABSTRACT
PURPOSE: Intraocular pressure is the main risk factor for glaucoma; however, additional risk factors may also matter. This systematic review and meta-analysis were conducted to summarize the evidence regarding the association of cholesterol parameters (total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels) and glaucoma. METHODS: Four electronic databases were searched for all publications containing 'glaucoma' and one of various forms of 'cholesterol' or 'lipoprotein'. Two independent reviewers screened abstracts and potentially full texts of identified articles for eligibility. Risk of bias was assessed with the Newcastle-Ottawa Scale. A random-effects meta-analysis was used to investigate the differences in total cholesterol, LDL and HDL levels between patients with and without glaucoma. RESULTS: Overall, 29 observational studies were included in the systematic review and 26 reported quantitative information to investigate differences in cholesterol parameters between patients with glaucoma (N = 7196) and patients without glaucoma (N = 350 441). Patients with glaucoma had significantly higher total cholesterol levels than patients without glaucoma (Mean Difference (MD) 7.9 mg/dl, 95% CI 3.3 to 12.5, p = 0.001) and lower mean HDL levels (MD -2.0 mg/dl, 95% CI: -3.1 to -0.9, p = 0.001). Patients with glaucoma had higher mean LDL levels than patients without glaucoma, albeit not statistically significant (MD 6.1 mg/dl, 95% CI: -4.3 to 16.4, p = 0.251). CONCLUSION: This systematic review and meta-analysis of observational studies found an association of glaucoma and high total cholesterol and low HDL levels, respectively. Although this supports the hypothesis that lipid levels pose an additional risk for glaucoma development, heterogeneity was substantial and causality cannot be presumed from identified observational studies.

[6] *Martínez-Quintana E, Rojas-Brito AB, Estupiñán-León H, Rodríguez-González F.* **Mediterranean diet adherence in patients with congenital heart disease**. American journal of cardiovascular disease 2020; 10:569-577.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33489460
ABSTRACT
The Mediterranean diet, based on a rural life where people ate what they grew, has shown cardiovascular benefits. Cross-sectional study of congenital heart disease (CHD) patients recruited consecutively from a single hospital outpatient clinic with the aim of determining their adherence to the Mediterranean diet according to the PREDIMED questionnaire. CHD complexity was categorized as simple, moderate, or great and demographic, clinical and blood test data were recorded. 200 CHD patients, median age 28 (16-54) years old and 120 (60%) males were studied. 45 (22.5%), 122 (61%) and 33 (16.5%) CHD patients had simple,

moderate, and great complexity defects respectively. PREDIMED score was classified as low (score 0-5), intermediate (6-9) or high (> 9). 146 (83%) CHD patients showed a suboptimal Mediterranean diet adherence (PREDIMED score < 9) with less than half of patients eating enough vegetables, fruits, legumes, fish or nuts but with a high intake of butter/margarine, commercial sweets and carbonated beverages. No significant differences were seen between sex, body mass index, cardiovascular risk factors, CHD complexity or the educational level and the PREDIMED scores. Only being married was associated with a significant lower Mediterranean diet adherence (P=0.019). Meanwhile, no statistical significance was observed between serum glucose, creatinine, uric acid, albumin, LDL cholesterol, HDL cholesterol or triglycerides levels according to the PREDIMED classification (low, intermediate or high adherence). Conclusions: CHD patients have a low adherence to the Mediterranean diet with a low intake of vegetables, fruits, legumes, and fish.

[7] *Poredos P, Visnovic Poredos A, Gregoric I*. **Endothelial Dysfunction and Its Clinical Implications**. Angiology 2021:3319720987752.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33504167
ABSTRACT
Endothelial dysfunction (ED) plays a substantial role in the pathogenesis of atherosclerosis and some other vascular diseases. ED has been demonstrated in patients with hypercholesterolemia, diabetes, smoking, hypertension, and in patients with atherosclerotic disease. Besides classical risk factors, ED is affected by chronic inflammatory diseases and acute infections, particularly viral diseases. Causes of ED include oxidative stress, inflammation, and shear stress, which decrease the bioavailability of nitric oxide. Markers of ED have been sought, particularly circulating markers. Using these tests, it is possible to evaluate the response to harmful effects of risk factors and the effects of treatment on vessel wall function. Endothelial dysfunction is significantly and directly correlated with the occurrence of cardiac events and the risk of cardiac events increase as ED worsens. Because endothelial function plays a central role in atherogenesis it became a therapeutic target. Endothelial dysfunction is reversible and its improvement may be achieved by elimination of risk factors, inhibitors of endothelium-derived contracting factors (angiotensin-converting enzyme), smoking cessation, lipid-lowering drugs, diet, and physical exercise. By reversing ED, it is possible to restore vascular function.

[8] *Li H, Xu QY, Xie Y et al.* **Effects of chronic HBV infection on lipid metabolism in non-alcoholic fatty liver disease: A lipidomic analysis**. Annals of hepatology 2021:100316.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33515803
ABSTRACT
INTRODUCTION AND OBJECTIVES: Chronic hepatitis B virus (HBV) infection exerts an impact on lipid metabolism, but its interaction with dysmetabolism-based non-alcoholic fatty liver disease (NAFLD) remains uncertain. Purpose of the study is to investigate the effects of HBV infection on lipid metabolism, hepatic steatosis and related impairments of NAFLD patients. METHODS: Biopsy-proven Chinese NAFLD patients with (NAFLD-HBV group, n = 21) or without chronic HBV infection (NAFLD group, n = 41) were enrolled in the case-control study. Their serum lipidomics was subjected to individual investigation by ultra-performance

liquid chromatography-tandem mass spectrometry. Steatosis, activity, and fibrosis (SAF) scoring revealed the NAFLD-specific pathological characteristics. RESULTS: Chronic HBV infection was associated with global alteration of serum lipidomics in NAFLD patients. Upregulation of phosphatidylcholine (PCs), choline plasmalogen (PC-Os) and downregulation of free fatty acids (FFAs), lysophosphatidylcholine (LPCs) dominated the HBV-related lipidomic characteristics. Compared to those of NAFLD group, the levels of serum hepatoxic lipids (FFA16:0, FFA16: 1, FFA18:1, FFA18:2) were significantly lowered in the NAFLD-HBV group. These low-level FFAs demonstrated correlation to statistical improvements in aspartate aminotransferase activity (FFA16:0, $r=0.33$; FFA16:1, $r=0.37$; FFA18:1, $r=0.32$; FFA18:2, $r=0.42$), hepatocyte steatosis (FFA16: 1, $r=0.39$; FFA18:1, $r=0.39$; FFA18:2, $r=0.32$), and ballooning (FFA16:0, $r=0.30$; FFA16:1, $r=0.45$; FFA18:1, $r=0.36$; FFA18:2, $r=0.30$) (all $P<0.05$). CONCLUSION: Chronic HBV infection may impact on the serum lipidomics and steatosis-related pathological characteristics of NAFLD.

[9] *Bergerot C, Angoulvant D, Lemesle G et al.* **It's never too early to beat your low-density lipoprotein cholesterol**. Archives of cardiovascular diseases 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33509745
ABSTRACT

[10] *Lyall DM, Ward J, Banach M et al.* **PCSK9 genetic variants and cognitive abilities: a large-scale Mendelian randomization study**. Archives of medical science : AMS 2021; 17:241-244.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33488877
ABSTRACT
INTRODUCTION: PCSK9 inhibitors lower low-density lipoprotein (LDL) cholesterol and are efficacious at reducing vascular disease, however questions remain about potential effects on cognitive function. METHODS: We examined the association of genetic variants in PCSK9 with continuous measures of cognitive ability in UK Biobank. Six independent polymorphisms in PCSK9 were used in up to 337,348 individuals. RESULTS: The PCSK9 allele score was associated with a lower risk of CHD, and weakly with worse log reaction time. CONCLUSIONS: We are unable to rule out meaningful associations of PCSK9 genetic variants with cognition, emphasising the potential need for continued pharmacovigilance for patients currently treated with PCSK9 inhibitors.

[11] *Nabi R, Alvi SS, Shah A et al.* **Ezetimibe attenuates experimental diabetes and renal pathologies via targeting the advanced glycation, oxidative stress and AGE-RAGE signalling in rats**. Archives of physiology and biochemistry 2021:1-16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33508970
ABSTRACT
The current in-vivo study was premeditated to uncover the protective role of ezetimibe (EZ) against advanced glycation endproducts (AGEs)-related pathologies in experimental diabetes. Our results showed that EZ markedly improved the altered biochemical markers of diabetes mellitus (DM) (FBG, HbA1c, insulin, microalbumin, and creatinine) and cardiovascular disease (in-vivo lipid/lipoprotein level and hepatic HMG-CoA reductase activity) along with diminished

plasma carboxymethyl-lysine (CML) and renal fluorescent AGEs level. Gene expression study revealed that EZ significantly down-regulated the renal AGEs-receptor (RAGE), nuclear factor-κB (NFκB-2), transforming growth factor-β (TGF-β1), and matrix metalloproteinase-2 (MMP-2) mRNA expression, however, the neuropilin-1 (NRP-1) mRNA expression was up-regulated. In addition, EZ also maintained the redox status via decreasing the lipid peroxidation and protein-bound carbonyl content (CC) and increasing the activity of high-density lipoprotein (HDL)-associated-paraoxonase-1 (PON-1) and renal antioxidant enzymes as well as also protected renal histopathological features. We conclude that EZ exhibits antidiabetic and reno-protective properties in diabetic rats.

[12] *Futema M, Ramaswami U, Tichy L et al.* **Comparison of the mutation spectrum and association with pre and post treatment lipid measures of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries**. Atherosclerosis 2021; 319:108-117.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33508743
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolaemia (FH) is commonly caused by mutations in the LDLR, APOB or PCSK9 genes, with untreated mean low density lipoprotein-cholesterol (LDL-C) concentrations being elevated in APOB mutation carriers, even higher in LDLR mutation and highest in those with a PCSK9 mutation. Here we examine this in children with FH from Norway, UK, The Netherlands, Belgium, Czech Republic, Austria, Portugal and Greece. METHODS: Differences in characteristics and pre- and post-treatment lipid concentrations in those with different molecular causes were compared by standard statistical tests. RESULTS: Data were obtained from 2866 children, of whom 2531 (88%) carried a reported LDLR/APOB/PCSK9 variant. In all countries, the most common cause of FH was an LDLR mutation (79% of children, 297 different), but the prevalence of the APOB p.(Arg3527Gln) mutation varied significantly (ranging from 0% in Greece to 39% in Czech Republic, $p < 2.2 \times 10(-16)$). The prevalence of a family history of premature CHD was significantly higher in children with an LDLR vs APOB mutation (16% vs 7% p=0.0005). Compared to the LDLR mutation group, mean (±SD) concentrations of pre-treatment LDL-C were significantly lower in those with an APOB mutation (n = 2260 vs n = 264, 4.96 (1.08)mmol/l vs 5.88 (1.41)mmol/l, $p < 2.2 \times 10(-16)$) and lowest in those with a PCSK9 mutation (n = 7, 4.71 (1.22)mmol/l). CONCLUSIONS: The most common cause of FH in children from eight European countries was an LDLR mutation, with the prevalence of the APOB p.(Arg3527Gln) mutation varying significantly across countries. In children, LDLR-FH is associated with higher concentrations of LDL-C and family history of CHD compared to those with APOB-FH.

[13] *Rubino J, MacDougall DE, Sterling LR et al.* **Combination of bempedoic acid, ezetimibe, and atorvastatin in patients with hypercholesterolemia: A randomized clinical trial**. Atherosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33514449
ABSTRACT

BACKGROUND AND AIMS: Many patients with hypercholesterolemia fail to achieve sufficient low-density lipoprotein cholesterol (LDL-C) lowering despite use of guideline-recommended lipid-lowering therapies. This study evaluated LDL-C lowering with the combination of bempedoic acid, ezetimibe, and atorvastatin. METHODS: This was a phase 2, randomized, double-blind, placebo-controlled study (NCT03051100). After washout of lipid-lowering drugs, patients were randomized 2:1 to triple therapy (bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg; n = 43) or placebo (n = 20) once daily for 6 weeks. The primary endpoint was percent change from baseline in LDL-C at week 6. RESULTS: Mean age for the 63 randomized patients was 61.2 years; baseline LDL-C was 154.8 mg/dL. At week 6, mean LDL-C lowering with triple therapy (-63.6%) was significantly greater than with placebo [-3.1%; difference, -60.5% [(95% CI, -68.0% to -53.0%); p < 0.001]. Significant reductions with triple therapy vs. placebo were also observed for non-high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein (p < 0.001 for all). With triple-therapy, 90% of patients achieved LDL-C <70 mg/dL and 95% of patients had ≥50% lower LDL-C from baseline to week 6; no patients in the placebo group met either goal. The majority of treatment-emergent adverse events were mild to moderate in severity. No patients experienced clinically relevant elevations in aminotransferase or creatine kinase levels. CONCLUSIONS: Among patients with hypercholesterolemia, the combination of bempedoic acid, ezetimibe, and atorvastatin significantly lowered LDL-C, allowing more than 90% of patients in this study to reach guideline-recommended LDL-C goals.

[14] *Vallejo-Vaz AJ, Packard CJ, Ference BA et al.* **LDL-cholesterol lowering and clinical outcomes in hypercholesterolemic subjects with and without a familial hypercholesterolemia phenotype: Analysis from the secondary prevention 4S trial**. Atherosclerosis 2021; 320:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33497862

ABSTRACT

BACKGROUND AND AIMS: Trial evidence for the benefits of cholesterol-lowering is limited for familial hypercholesterolemia (FH) patients, since they have not been the focus of large outcome trials. We assess statin use in coronary artery disease (CAD) subjects with low-density lipoprotein cholesterol (LDL-C) ≥4.9 mmol/L with or without an FH phenotype. METHODS: The 4S trial randomized hypercholesterolemic CAD patients to simvastatin or placebo. We first stratified participants into baseline LDL-C <4.9 and ≥ 4.9 mmol/L; next, based on the DLCN criteria for FH, the latter group was stratified into four subgroups by presence of none, one or both of "premature CAD" and "family history of CAD". Participants having both are defined as having an FH phenotype. RESULTS: 2267 and 2164 participants had LDL-C <4.9 and ≥ 4.9 mmol/L, respectively. Mortality endpoints and major coronary events (MCE) were significantly reduced with simvastatin versus placebo in both groups over 5.4 years, but the latter derived greater absolute risk reductions (ARR) (4.1-4.3% for mortality endpoints, versus 2.5-2.8%). LDL-C reductions were similar among the 4 subgroups with levels ≥4.9 mmol/L. Participants with FH phenotype (n = 152) appeared to derive greater relative benefits with simvastatin than the other three subgroups (all-cause death: 84% relative risk reduction, p = 0.046; MCE: 55% reduction, p = 0.0297); statistical interaction was non-significant. Participants with FH phenotype derived greater ARR than any other group with

simvastatin versus placebo (all-cause mortality: 6.6% ARR; MCE 13.2%; versus 3.8% and 8.3%, respectively, among participants with LDL-C ≥4.9 mmol/L but without features suggestive of FH). CONCLUSIONS: The FH phenotype appeared to be associated with greater clinical benefits from a given magnitude of LDL-C reduction as compared to individuals without FH phenotype.

[15] *Lenz M, Kaun C, Krychtiuk KA et al.* **Effects of Nicorandil on Inflammation, Apoptosis and Atherosclerotic Plaque Progression**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33513743

ABSTRACT

Nicorandil, a balanced vasodilator, is used in the second-line therapy of angina pectoris. In this study, we aimed to illuminate the effects of nicorandil on inflammation, apoptosis, and atherosclerotic plaque progression. Twenty-five LDL-R -/- mice were fed a high-fat diet for 14 weeks. After 6 weeks mice were randomly allocated to treatment with nicorandil (10 mg/kg/day) or tap water. Nicorandil treatment led to a more stable plaque phenotype, displaying an increased thickness of the fibrous cap (p = 0.014), a significant reduction in cholesterol clefts (p = 0.045), and enhanced smooth muscle cell content (p = 0.009). In endothelial cells nicorandil did not reduce the induction of adhesion molecules or proinflammatory cytokines. In H(2)O(2) challenged endothelial cells, pretreatment with nicorandil significantly reduced the percentage of late apoptotic/necrotic cells (p = 0.016) and the ratio of apoptotic to living cells (p = 0.036). Atherosclerotic lesions of animals treated with nicorandil exhibited a significantly decreased content of cleaved caspase-3 (p = 0.034), lower numbers of apoptotic nuclei (p = 0.040), and reduced 8-oxogunanine staining (p = 0.039), demonstrating a stabilizing effect of nicorandil in established atherosclerotic lesions. We suggest that nicorandil has a positive effect on atherosclerotic plaque stabilization by reducing apoptosis.

[16] *Orsi E, Penno G, Solini A et al.* **Independent association of atherogenic dyslipidaemia with all-cause mortality in individuals with type 2 diabetes and modifying effect of gender: a prospective cohort study**. Cardiovascular diabetology 2021; 20:28.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33516215

ABSTRACT

BACKGROUND: Atherogenic dyslipidaemia has been implicated in the residual risk for cardiovascular morbidity and mortality, which remains despite attainment of LDL cholesterol goals especially in individuals with type 2 diabetes. However, its relationship with all-cause death has not been sufficiently explored. This analysis evaluated the independent association of increased triglycerides and triglyceride:HDL cholesterol ratio (TG:HDL) and decreased HDL cholesterol with total mortality and the possible modifying effect of gender in a large cohort of patients with type 2 diabetes. METHODS: This observational, prospective study enrolled 15,773 patients in 19 Diabetes Clinics throughout Italy in the years 2006-2008. Triglycerides and total and HDL cholesterol were measured by colorimetric enzymatic methods. Vital status was retrieved on 31 October 2015 for 15,656 patients (99.3%). Participants were stratified by quartiles of triglycerides, HDL cholesterol, and TG:HDL. RESULTS: There were 3,602 deaths over a follow-up 7.42 ± 2.05 years (31.0 × 1000 person-years). In the unadjusted analyses, the

highest TG:HDL (but not triglyceride) and the lowest HDL cholesterol quartile were associated with increased death rate and mortality risk. When sequentially adjusting for confounders, including total, LDL, or non-HDL cholesterol and lipid-lowering treatment, mortality risk was significantly higher in the highest triglyceride (hazard ratio 1.167 [95% confidence interval 1.055-1.291], p = 0.003) and TG:HDL (1.192 [1.082-1.314], p < 0.0001) and the lowest HDL cholesterol (1.232 [1.117-1.360], p < 0.0001) quartile, though the association of triglycerides and HDL cholesterol disappeared after further adjustment for each other. Interaction with gender was significant only for HDL cholesterol (p = 0.0009). The relationship with death was stronger for triglycerides in males and HDL cholesterol in females, with these associations remaining significant even after adjustment for HDL cholesterol (1.161 [1.019-1.324], p = 0.025, for the highest vs the lowest triglyceride quartile) and triglycerides (1.366 [1.176-1.587], p < 0.0001, for the lowest vs the highest HDL cholesterol quartile). CONCLUSIONS: In patients with type 2 diabetes, higher triglycerides and TG:HDL and lower HDL cholesterol were independently associated with increased all-cause mortality, with a modifying effect of gender for triglycerides and HDL cholesterol. These data suggest that atherogenic dyslipidaemia, especially TG:HDL, may serve as predictor of all-cause death in these individuals. Trial registration ClinicalTrials.gov, NCT00715481, 15 July, 2008.

[17] *Susekov AV, Korol LA, Watts GF*. **Bempedoic Acid in the Treatment of Patients with Dyslipidemias and Statin Intolerance**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33502687

ABSTRACT

An elevated plasma low-density lipoprotein cholesterol (LDL-C) level is a well-established atherosclerotic cardiovascular disease (ACSVD) risk factor. Randomized studies with statins (alone or in combination with other lipid-lowering drugs) have demonstrated their clinical efficacy in lowering LDL-C. Several classes of new, non-statin agents have been successfully studied and used (e.g., ezetimibe and inhibitors of proprotein convertase subtilisin/kexin type 9 [i-PSCK9]). However, many high ACSVD risk patients remain at a high residual cardiovascular risk, with at least 10% being statin intolerant. Bempedoic acid (ETC-1002) is a new inhibitor of cholesterol synthesis that targets ATP citrate lyase (ACL). Importantly, ETC-1002 is only converted into an active form in the liver and is free of muscle side effects.Area Covered: Mechanism of action of ETC-1002, clinical pharmacology, completed clinical studies with bempedoic acid, lipid-lowering efficacy/safety issues, and recent meta-analyses of trials with ETC-1002.Expert Opinion: ETC-1002 has been extensively studied in phase I-III clinical studies in over 4000 individuals from different patient populations (statin intolerance, familial hypercholesterolemia, and high ACSVD risk patients), ETC-1002 has been demonstrated to have moderate cholesterol-lowering efficacy and a good safety profile at a dose of 180 mg/day as a monotherapy and in combination with statins and ezetimibe. The ongoing study CLEAR Outcomes, with composite cardiovascular endpoints, will elucidate the role of bempedoic acid in the management of high ACSVD risk and statin-intolerant patients with hypercholesterolemia. Long-term safety data on bempedoic acid are needed to fully establish this agent in evidence-informed guidelines for managing of patients with dyslipidemias.

[18] *Loving BA, Tang M, Neal MC et al.* **Lipoprotein Lipase Regulates Microglial Lipid Droplet Accumulation**. Cells 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33498265
ABSTRACT
Microglia become increasingly dysfunctional with aging and contribute to the onset of neurodegenerative disease (NDs) through defective phagocytosis, attenuated cholesterol efflux, and excessive secretion of pro-inflammatory cytokines. Dysfunctional microglia also accumulate lipid droplets (LDs); however, the mechanism underlying increased LD load is unknown. We have previously shown that microglia lacking lipoprotein lipase (LPL KD) are polarized to a pro-inflammatory state and have impaired lipid uptake and reduced fatty acid oxidation (FAO). Here, we also show that LPL KD microglia show excessive accumulation of LD-like structures. Moreover, LPL KD microglia display a pro-inflammatory lipidomic profile, increased cholesterol ester (CE) content, and reduced cholesterol efflux at baseline. We also show reduced expression of genes within the canonical cholesterol efflux pathway. Importantly, PPAR agonists (rosiglitazone and bezafibrate) rescued the LD-associated phenotype in LPL KD microglia. These data suggest that microglial-LPL is associated with lipid uptake, which may drive PPAR signaling and cholesterol efflux to prevent inflammatory lipid distribution and LD accumulation. Moreover, PPAR agonists can reverse LD accumulation, and therefore may be beneficial in aging and in the treatment of NDs.

[19] *Armario P, Brotons C, Elosua R et al.* **Statement of the Spanish Interdisciplinary Vascular Prevention Committee on the updated European Cardiovascular Prevention Guidelines**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33495044
ABSTRACT
We present the adaptation for Spain of the updated European Cardiovascular Prevention Guidelines. In this update, greater stress is laid on the population approach, and especially on the promotion of physical activity and healthy diet through dietary, leisure and active transport policies in Spain. To estimate vascular risk, note should be made of the importance of recalibrating the tables used, by adapting them to population shifts in the prevalence of risk factors and incidence of vascular diseases, with particular attention to the role of chronic kidney disease. At an individual level, the key element is personalised support for changes in behaviour, adherence to medication in high-risk individuals and patients with vascular disease, the fostering of physical activity, and cessation of smoking habit. Furthermore, recent clinical trials with PCSK9 inhibitors are reviewed, along with the need to simplify pharmacological treatment of arterial hypertension to improve control and adherence to treatment. In the case of patients with type 2 diabetes mellitus and vascular disease or high vascular disease risk, when lifestyle changes and metformin are inadequate, the use of drugs with proven vascular benefit should be prioritised. Lastly, guidelines on peripheral arterial disease and other specific diseases are included, as is a recommendation against prescribing antiaggregants in primary prevention.

[20] *Miao Z, Schultzberg M, Wang X, Zhao Y*. **Role of polyunsaturated fatty acids in ischemic stroke - A perspective of specialized pro-resolving mediators**. Clinical nutrition (Edinburgh, Scotland) 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33509668
ABSTRACT
Polyunsaturated fatty acids (PUFAs) have been proposed as beneficial for cardiovascular health. However, results from both epidemiological studies and clinical trials have been inconsistent, whereas most of the animal studies showed promising benefits of PUFAs in the prevention and treatment of ischemic stroke. In recent years, it has become clear that PUFAs are metabolized into various types of bioactive derivatives, including the specialized pro-resolving mediators (SPMs). SPMs exert multiple biofunctions, such as to limit excessive inflammatory responses, regulate lipid metabolism and immune cell functions, decrease production of pro-inflammatory factors, increase anti-inflammatory mediators, as well as to promote tissue repair and homeostasis. Inflammation has been recognised as a key contributor to the pathophysiology of acute ischemic stroke. Owing to their potent pro-resolving actions, SPMs are potential for development of novel anti-stroke therapy. In this review, we will summarize current knowledge of epidemiological studies, basic research and clinical trials concerning PUFAs in stroke prevention and treatment, with special attention to SPMs as the unsung heroes behind PUFAs.

[21] *Eastman AJ, Moore RE, Townsend SD et al.* **The Influence of Obesity and Associated Fatty Acids on Placental Inflammation**. Clinical therapeutics 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33487441
ABSTRACT
PURPOSE: Maternal obesity, affecting nearly 1 in 4 pregnancies, is associated with increased circulating saturated fatty acids, such as palmitate. These fatty acids are implicated in placental inflammation, which may in turn exacerbate both maternal-fetal tolerance and responses to pathogens, such as group B Streptococcus. In this review, we address the question, "How do obesity and associated fatty acids influence placental inflammation?" METHODS: In this narrative review, we searched PubMed and Google Scholar using combinations of the key words placental inflammation or pregnancy and lipids, fatty acids, obesity, palmitate, or other closely related search terms. We also used references found within these articles that may have been absent from our original search queries. We analyzed methods and key results of these articles to compare and contrast their findings, which were occasionally at odds with each other. FINDINGS: Although obesity can be studied as a whole, complex phenomena with in vivo mouse models and human samples from patients with obesity, in vitro modeling often relies on the treatment of cells or tissues with ≥1 fatty acids and occasionally other compounds (eg, glucose and insulin). We found that palmitate, most commonly used in vitro to recreate hallmarks of obesity, induces apoptosis, oxidative stress, mitochondrial dysfunction, autophagy defects, and inflammasome activation in many placental cell types. We compare this to in vivo models of obesity wherever possible. We found that obesity as a whole may have more complex regulation of these phenomena (apoptosis, oxidative stress, mitochondrial dysfunction, autophagy defects, and inflammasome activation) compared with in vitro models of fatty acid treatment (primarily palmitate) because of the

presence of unsaturated fatty acids (ie, oleate), which may have anti-inflammatory effects. IMPLICATIONS: The interaction of unsaturated fatty acids with saturated fatty acids may ameliorate many inflammatory effects of saturated fatty acids alone, which complicates interpretation of in vitro studies that focus on a particular fatty acid in isolation. This complication may explain why certain studies of obesity in vivo have differing outcomes from studies of specific fatty acids in vitro.

[22] *Gorabi AM, Ghanbari M, Sathyapalan T et al.* **Implications of microRNAs in the pathogenesis of atherosclerosis and prospects for therapy**. Current drug targets 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33494668

ABSTRACT

MicroRNAs (miRNAs) are non-coding RNAs containing around 22 nucleotides, which are expressed in vertebrates and plants. They act as posttranscriptional gene expression regulators, fine-tuning various biological processes in different cell types. There is emerging evidence on their role in different stages of atherosclerosis. In addition to regulating the inflammatory cells involved in atherosclerosis, miRNAs play fundamental roles in the pathophysiology of atherosclerosis such as endothelial cell (EC) dysfunction, the aberrant function of the vascular smooth muscle cell (VSMC) and cholesterol metabolism. Moreover, miRNAs participate in several pathogenic pathways of atherosclerotic plaque development, including their effects on immune cell signaling receptors and lipid uptake. In this study, we review our current knowledge of the regulatory role of miRNAs in various pathogenic pathways underlying atherosclerosis development and also outline potential clinical applications of miRNAs in atherosclerosis.

[23] *Qi YY, Yan L, Wang ZM et al.* **Comparative efficacy of pharmacological agents on reducing the risk of major adverse cardiovascular events in the hypertriglyceridemia population: a network meta-analysis**. Diabetology & metabolic syndrome 2021; 13:15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33514420

ABSTRACT

BACKGROUND: Hypertriglyceridemia (HTG) is considered an independent risk factor for major adverse cardiovascular events (MACE). METHODS: This study analyzed the effects of various agents on MACE risk reduction in HTG (serum triglyceride ≥ 150 mg/dl) populations by performing a network meta-analysis. We performed a frequentist network meta-analysis to conduct direct and indirect comparisons of interventions. PubMed, EMBASE, and the Cochrane library were searched for trials until Jul 6, 2020. Randomized controlled trials that reported MACE associated with agents in entire HTG populations or in subgroups were included. The primary outcome was MACE. RESULTS: Of the 2005 articles screened, 21 trials including 56,471 patients were included in the analysis. The network meta-analysis results for MACE risk based on frequency data showed that eicosapentaenoic acid (EPA) (OR: 1.32; 95% CI 1.19-1.46), gemfibrozil (OR: 1.53; 95% CI 1.20-1.95), niacin plus clofibrate (OR: 2.00; 95% CI 1.23-3.25), pravastatin (OR: 1.32; 95% CI 1.15-1.52), simvastatin (OR: 2.38; 95% CI 1.55-3.66), and atorvastatin (OR: 0.55; 95% CI 0.37-0.82) significantly reduced the risk of MACE compared to the control conditions. In the subgroup analysis of HTG patients with triglycerides ≥ 200 mg/dL, bezafibrate (OR: 0.56; 95% CI 0.33-0.94), EPA (OR: 0.72; 95% CI

0.62-0.82), and pravastatin (OR: 1.33; 95% CI 1.01-1.75) significantly reduced the MACE risk. CONCLUSIONS: Simvastatin had a clear advantage in reducing the risk of MACE in the entire HTG population analyzed in this meta-analysis. EPA, but not omega-3 fatty acid, was considered an effective HTG intervention. Among fibrates, gemfibrozil was most effective, though bezafibrate may significantly reduce the risk of MACE in populations with triglyceride levels of 200-300 mg/dL. Trial registration retrospectively registered in PROSPERO (CRD42020213705).

[24] *El-Eshmawy MM, Mahsoub N, Asar M, Elsehely I*. **Association Between Total Bilirubin Levels and Cardio-metabolic Risk Factors Related to Obesity**. Endocrine, metabolic & immune disorders drug targets 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33511960
ABSTRACT
BACKGROUND: The link between bilirubin and cardiometabolic outcomes has been previously identified with positive health effects of mild hyperbilirubinaemia. On the other hand, recent evidence has suggested an association between low circulating bilirubin levels and obesity. This study was conducted to assess the association of total bilirubin levels with metabolic and cardiovascular risk factors related to obesity. METHODS: A total of 50 obese adults and 50 healthy controls matched for age and sex were enrolled in this study. Anthropometric measurements, fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), HOMA- β (%), lipids profile, monocyte to lymphocyte ratio (MLR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), uric acid, gamma glutamyl transpeptidase (GGT), AST/ALT ratio and total bilirubin were assessed. RESULTS: Total bilirubin, high density lipoprotein cholesterol (HDL-C) and AST/ALT ratio were significantly lower, whereas fasting insulin, HOMA-IR, total cholesterol, triglycerides, low density lipoprotein cholesterol, NLR, uric acid and GGT were significantly higher in obese adults than in healthy controls. Bilirubin was negatively associated with body mass index, waist circumference, fasting insulin, HOMA-IR, NLR, PLR, uric acid, and positively associated with HDL-C. HDL-C and NLR were the independent predictor variables of total bilirubin. CONCLUSION: Among all the studied cardio-metabolic risk factors, HDL-C and NRL are the most closely associated variables with total bilirubin levels in obese adults.

[25] *Hong H, Xu Y, Xu J et al.* **Cadmium exposure impairs pancreatic β-cell function and exaggerates diabetes by disrupting lipid metabolism**. Environ Int 2021; 149:106406.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33508533
ABSTRACT
Cadmium is known as an environmental pollutant that contributes to pancreatic damage and the pathogenesis of diabetes. However, less attention has been devoted to elucidating the mechanisms underlying Cd-induced pancreatic β-cell dysfunction and the role of Cd toxicity in the development of diabetes. In this study, we demonstrated that exposure to Cd caused remarkable pancreatic β-cell dysfunction and death, both in vitro and in vivo. Lipidomic analysis of Cd-exposed pancreatic β-cells using high-resolution mass spectrometry revealed that Cd exposure altered the profile and abundance of lipids. Cd exposure induced intracellular lipid accumulation, promoted lipid biogenesis, elevated pro-inflammatory lipid contents and

inhibited lipid degradation. Furthermore, Cd exposure upregulated the expression levels of TNF-α, IL-1β and IL-6 in pancreatic β-cells and elevated the TNF-α, IL1-β and IL-6 levels in the serum and pancreas. Taken together, the results of our study demonstrated that environmental relevant Cd exposure causes pro-inflammatory lipids elevation and insulin secretion dysfunction in β-cells and hence exaggerates diabetes development. Combined exposure to environmental hazardous chemicals might markedly increase the probability of developing diabetes in humans. This study provides new metabolic and pharmacological targets for antagonizing Cd toxicity.

[26] *Lian Z, Song JX, Yu SR et al.* **Therapeutic targets of rosuvastatin on heart failure and associated biological mechanisms: A study of network pharmacology and experimental validation**. European journal of pharmacology 2021; 895:173888.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33493484
ABSTRACT
To explore the potential targets underlying the effect of rosuvastatin on heart failure (HF) by utilizing a network pharmacology approach and experiments to identify the results. PharmMapper and other databases were mined for information relevant to the prediction of rosuvastatin targets and HF-related targets. Then, the rosuvastatin-HF target gene networks were created in Cytoscape software. Eventually, the targets and enriched pathways were examined by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Furthermore, we constructed an HF animal model and used rosuvastatin to treat them, identifying the changes in heart function and related protein expression. We further used different cells to explore the mechanisms of rosuvastatin. Thirty-five intersection targets indicated the therapeutic targets linked to HF. GO analysis showed that 481 biological processes, 4 cellular components and 23 molecular functions were identified. KEGG analysis showed 13 significant treatment pathways. In animal experiments, rosuvastatin significantly improved the cardiac function of post-myocardial infarction mice and prevented the development of HF after myocardial infarction by inhibiting IL-1B expression. Cell experiments showed that rosuvastatin could reduce the expression of IL-1B in HUVEC and THP-1 cells. The therapeutic mechanism of rosuvastatin against HF may be closely related to the inhibition of the expression of apoptosis-related proteins, inflammatory factors, and fibrosis-related genes. However, IL-1B is one of the most important target genes.

[27] *Lee GE, Kim J, Lee JS et al.* **Role of Proprotein Convertase Subtilisin/Kexin Type 9 in the Pathogenesis of Graves' Orbitopathy in Orbital Fibroblasts**. Frontiers in endocrinology 2020; 11:607144.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33488522
ABSTRACT
BACKGROUND: The proprotein convertase subtilisin/kexin type 9 (PCSK9) has been implicated in the pathogenesis of inflammatory diseases. We sought to investigate the role of PCSK9 in the pathogenesis of Graves' orbitopathy (GO) and whether it may be a legitimate target for treatment. METHODS: The PCSK9 was compared between GO (n=11) and normal subjects (n=7) in orbital tissue explants using quantitative real-time PCR, and in cultured interleukin-1β (IL-1β)-treated fibroblasts using western blot. Western blot was used to identify

the effects of PCSK9 inhibition on IL-1β-induced pro-inflammatory cytokines production and signaling molecules expression as well as levels of adipogenic markers and oxidative stress-related proteins. Adipogenic differentiation was identified using Oil Red O staining. The plasma PCSK9 concentrations were compared between patients with GO (n=44) and healthy subjects (n=26) by ELISA. RESULTS: The PCSK9 transcript level was higher in GO tissues. The depletion of PCSK9 blunted IL-1β-induced expression of intercellular adhesion molecule 1 (ICAM-1), IL-6, IL-8, and cyclooxygenase-2 (COX-2) in GO and non-GO fibroblasts. The levels of activated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and phosphorylated forms of Akt and p38 were diminished when PCSK9 was suppressed in GO fibroblasts. Decreases in lipid droplets and attenuated levels of peroxisome proliferator-activated receptor gamma (PPARγ), CCAAT/enhancer-binding protein β (C/EBPβ), and leptin as well as hypoxia-inducible factor 1α (HIF-1α), manganese superoxide dismutase (MnSOD), thioredoxin (Trx), and heme oxygenase-1 (HO-1) were noted when PCSK9 was suppressed during adipocyte differentiation. The plasma PCSK9 level was significantly higher in GO patients and correlated with level of thyrotropin binding inhibitory immunoglobulin (TBII) and the clinical activity score (CAS). CONCLUSIONS: PCSK9 plays a significant role in GO. The PCSK9 inhibition attenuated the pro-inflammatory cytokines production, oxidative stress, and fibroblast differentiation into adipocytes. PCSK9 may serve as a therapeutic target and biomarker for GO.

[28] *Xu B, Li S, Fang Y et al.* **Proprotein Convertase Subtilisin/Kexin Type 9 Promotes Gastric Cancer Metastasis and Suppresses Apoptosis by Facilitating MAPK Signaling Pathway Through HSP70 Up-Regulation**. Frontiers in oncology 2020; 10:609663.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33489919

ABSTRACT

OBJECTIVE: To examine the effect of proprotein convertase subtilisin/kexin type 9 (PCSK9) on gastric cancer (GC) progression and prognosis, and to explore the underlying mechanism. METHODS: PCSK9 expression levels in human GC tissues were determined by quantitative real-time PCR, western blotting, and immunohistochemical assay. PCSK9 serum levels were detected by enzyme-linked immunosorbent assay. The relationships of PCSK9 and GC progression and survival were analyzed using the Chi-square test, Kaplan-Meier analysis, and Cox proportional hazards model. The effect of PCSK9 on cell invasion, migration, and apoptosis were determined in human GC cell lines and mouse xenograft model separately using PCSK9 knockdown and overexpression strategies. The PCSK9 interacting molecules, screened by co-immunoprecipitation combined with LC-MS/MS, were identified by immunofluorescence localization and western blotting. Additionally, the mitogen-activated protein kinase (MAPK) pathway was assessed by western blotting. RESULTS: PCSK9 mRNA and protein levels were significantly elevated in GC tissues compared with the paired normal tissues at our medical center ($P < 0.001$). Notably, the up-regulation of PCSK9 expression in GC tissues was related to tumor progression and poor survival. GC patients had higher serum levels of PCSK9 than the age-matched healthy controls ($P < 0.001$); PCSK9 promoted invasive and migratory ability and inhibited apoptosis in GC cells with no apparent affection in cell proliferation. The silencing of PCSK9 reversed these effects, suppressing tumor metastasis in vitro and in vivo. Furthermore, PCSK9 maintained these functions through up-

regulating heat shock protein 70 (HSP70), ultimately facilitating the mitogen-activated protein kinase (MAPK) pathway. CONCLUSION: Collectively, our data revealed that high PCSK9 expression levels in GC tissue were correlated with GC progression and poor prognosis and that PCSK9 could promote GC metastasis and suppress apoptosis by facilitating MAPK signaling pathway through HSP70 up-regulation. PCSK9 may represent a novel potential therapeutic target in GC.

[29] *van Asch B, Teixeira da Costa LF*. **Patterns and tempo of PCSK9 pseudogenizations suggest an ancient divergence in mammalian cholesterol homeostasis mechanisms**. Genetica 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33515402
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a central role in cholesterol homeostasis in humans as a major regulator of LDLR levels. PCSK9 is an intriguing protease in that it does not act by proteolysis but by preventing LDLR recirculation from endosomes to the plasma membrane. This, and the inexistence of any other proteolytic substrate but itself could suggest that PCSK9 is an exquisite example of evolutionary fine-tuning. However, the gene has been lost in several mammalian species, and null alleles are present (albeit at low frequencies) in some human populations without apparently deleterious health effects, raising the possibility that the PCSK9 may have become dispensable in the mammalian lineage. To address this issue, we systematically recovered, assembled, corrected, annotated and analysed publicly available PCSK9 sequences for 420 eutherian species to determine the distribution, frequencies, mechanisms and timing of PCSK9 pseudogenization events, as well as the evolutionary pressures underlying the preservation or loss of the gene. We found a dramatic difference in the patterns of PCSK9 retention and loss between Euarchontoglires-where there is strong pressure for gene preservation-and Laurasiatheria, where multiple independent events have led to PCSK9 loss in most species. These results suggest that there is a fundamental difference in the regulation of cholesterol metabolism between Euarchontoglires and Laurasiatheria, which in turn has important implications for the use of Laurasiatheria species (e.g. pigs) as animal models of human cholesterol-related diseases.

[30] *Park Y, Kim TJ, Lee H et al.* **Eradication of Helicobacter pylori infection decreases risk for dyslipidemia: A cohort study**. Helicobacter 2021:e12783.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33508177
ABSTRACT
BACKGROUND: Previous studies have suggested a relationship between Helicobacter pylori infection and dyslipidemia; however, large-scale longitudinal studies have not elucidated this association. This study assessed the longitudinal effects of H. pylori infection and eradication on lipid profiles in a large cohort. METHODS: This cohort study included 2,626 adults without dyslipidemia at baseline, who participated in a repeated, regular health-screening examination, which included upper gastrointestinal endoscopy, between January 2009 and December 2018. The primary outcome was incident dyslipidemia at follow-up. RESULTS: During the 10,324 person-years of follow-up, participants with persistent H. pylori infection had a higher incidence rate (130.5 per 1,000 person-years) of dyslipidemia than those whose infections had been

successfully controlled (98.1 per 1,000 person-years). In a multivariable model adjusted for age, sex, waist circumference, smoking status, alcohol intake, and education level, the H. pylori eradication group was associated with a lower risk of dyslipidemia than the persistent group (HR, 0.85; 95% CI, 0.77-0.95; p = 0.004). The association persisted after further adjustment for baseline levels of low-density and high-density lipoprotein cholesterol (HR, 0.87; 95% CI, 0.79-0.97; p = 0.014). CONCLUSIONS: H. pylori infection may play a pathophysiologic role in the development of dyslipidemia, whereas H. pylori eradication might decrease the risk of dyslipidemia.

[31] *El-Sehrawy AA, State O, Elzehery RR, Mohamed AS*. **Insulin Resistance and Non-Alcoholic Fatty Liver Disease in Premenopausal Women with Metabolic Syndrome**. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2021; 53:100-104.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33513642
ABSTRACT
It is suggested that estrogen protects premenopausal women against non-alcoholic fatty liver disease. From another perspective, the relation between metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD) is bidirectional. Role of insulin resistance (IR) in NAFLD continues to be a matter of debate. The present study aimed to assess the relation between IR and NAFLD in premenopausal women with MetS. The study included 51 premenopausal women with MetS. In addition, there were 40 age-matched healthy controls. All participants were subjected to careful history taking and thorough clinical examination. Performed laboratory investigations included fasting blood glucose, fasting insulin, lipid profile, and liver functions. Calculation of IR was achieved by the Homeostasis Model Assessment (HOMA-IR). NAFLD was graded into three grades according to findings of abdominal ultrasound. Patients had significantly higher BMI, SBP, DBP, FBG, fasting insulin, HOMA-IR, total cholesterol, triglycerides, and LDL levels when compared with controls. They also had significantly lower HDL levels in comparison to controls. Moreover, they have more advanced grades of NAFLD in contrast to controls. Comparison between patients with various grades of NAFLD regarding the clinical data revealed significant increase of fasting insulin and HOMA-IR levels with advancing NAFLD grade. Using multivariate regression analysis, HOMA-IR was an independent predictor of advanced NAFLD grade. In conclusion, the present study documented a combined inter-relation between MetS, IR, and NAFLD in premenopausal women with MetS. IR is correlated with NAFLD grade.

[32] *Majeed ML, Ghafil FA, Fatima G et al.* **Anti-Atherosclerotic and Anti-Inflammatory Effects of Curcumin on Hypercholesterolemic Male Rabbits**. Indian journal of clinical biochemistry : IJCB 2021; 36:74-80.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33505130
ABSTRACT
Curcumin has a potent antioxidant and anti-inflammatory properties that may suppress inflammatory component of atherosclerosis. It has been demonstrated that curcumin derivatives can reduce the formation of arterial fatty streaks in cholesterol-fed rabbits. Therefore in this study we evaluated the protective effects of Curcumin on the progression of

atherosclerosis. 20 mature rabbits were included for this study; they were randomly divided into four groups each of 5. Group 1: (normal control) were fed corn pellets diet and tab water, group 2: (high cholesterol diet control) were kept on cholesterol rich diet (2% cholesterol) and tab water. Group 3: (cholesterol and rosuvastatin treated group) were kept on cholesterol rich diet (2% cholesterol) and 2.5 mg/kg/day Rosuvastatin dispersed in DW and given orally, group 4: (cholesterol and curcumin treated group) were kept on cholesterol rich diet (2% cholesterol) and 0.2% curcumin added with corn pellets. The study continued for 12 weeks then assessment of serum level of high sensitive C-reactive protein, ICAM1, VCAM1 and PCSK9 was carried out at the end of the study. Total antioxidant activity of curcumin was also determined. Histopathological examination of aortic tissues for atherosclerotic changes was also carried out. Atherogenic (cholesterol rich diet) induced an increment in serum level of TC, LDL, VLDL and TG with concomitant decrement in serum level of HDL and increased atherogenic index. Treatment with curcumin produced substantial reduction in serum TC, LDL, TG with no effect on HDL level thus decreased atherogenic index. Rabbits treated with curcumin showed a significant reduction in the serum level of high sensitive C-reactive protein, ICAM1, VCAM, PCSK9 serum expression and aortic total antioxidant capacity. Curcumin has a potent anti-inflammatory and anti- oxidant effects against atherosclerosis so exerts a protective role by decreasing lipid oxidation and inflammatory markers.

[33] *Kim GM, Kim BK, Kim DR et al.* **An Association between Lower Extremity Function and Cognitive Frailty: A Sample Population from the KFACS Study**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33498760

ABSTRACT

The present study aimed to define the physical function and lipid profile for physical and cognitive frailty in community-dwelling Korean older adults. A total of 229 participants (age = 76.76 ± 3.72 years; body mass index = 24.83 ± 3.15) were classified into four groups: robust, pre-frailty, cognitive decline, and cognitive frailty. An analysis on the four groups was performed to measure their physical and cognitive function, as well as blood biomarkers. The area under (AUC) the receiver operating characteristic curve (ROC) indicated that the 6-min Walk Test (6MWT), Timed Up and Go test (TUG), and Five Times Sit-to-Stand test (FTSS) had the potential to distinguish the capacity of an old adult to predict cognitive frailty. The 6MWT had a higher sensitivity and the TUG and FTSS tests had greater specificity. With cognitive frailty as a categorical variable, cognitive frailty status was a significant predictor of the TUG (odds ratio (OR) 2.897; 95% confidence interval (CI), 1.283-6.541), FTSS (OR 3.337; 95% CI 1.451-7.673), and 6MWT (OR 0.204; 95% CI 0.070-0.591) tests. Our findings indicate that the 6MWT, TUG, and FTSS tests are closely related to cognitive frailty and can provide potential prognostic cutoff points.

[34] *Ibdah RK, Al-Eitan LN, Alrabadi NN et al.* **Impact of PCSK9, WDR12, CDKN2A, and CXCL12 Polymorphisms in Jordanian Cardiovascular Patients on Warfarin Responsiveness and Sensitivity**. International journal of general medicine 2021; 14:103-118.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33488114

ABSTRACT
BACKGROUND: The main objective of this study is sought to determine the impacts of PCSK9, WDR12, CDKN2A, and CXCL12 polymorphisms on warfarin sensitivity and responsiveness in Jordanian cardiovascular patients during the initiation and stabilization phases of therapy. METHODS: This study took place at the anticoagulation clinic at Queen Alia Heart Institute (QAHI) in Jordan. DNA samples were collected from 212 cardiovascular patients and 213 healthy controls. Genomic SNPs genotyping was conducted using the MassARRAY System at the Australian Genome Research Facility. RESULTS: This study assessed 10 polymorphisms (rs11206510 within the PCSK9 gene, rs6725887 and rs7582720 within the WDR12 gene, rs4977574, rs10757278, and rs1333049 within the CDKN2A gene, rs2862116, rs7906426, rs1746048, and rs268322 within the CXCL12 gene) in 212 Jordanian cardiovascular patients. Carriers of CDKN2A rs1333049, rs10757278, and PCSK9 rs11206510 polymorphisms had an increased risk of resistance during the initiation phase of warfarin therapy compared to those who do not carry it, or those who are carrying one polymorphism only ($P < 0.05$), while carriers of CXCL12 rs7906426 polymorphism had similar increased risk but during the stabilization phase of warfarin therapy ($P < 0.05$). CONCLUSION: Carriers of CXCL12 rs2862116 polymorphism had an increased risk to be warfarin extensive responders compared to those with no or only one polymorphism ($P = 0.01$). However, the presence of PCSK9 rs11206510 polymorphism affects the warfarin maintenance doses ($P > 0.0001$).

[35] *Jenkins DJA, Spence JD, Giovannucci EL et al.* **Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment: JACC Focus Seminar**. Journal of the American College of Cardiology 2021; 77:423-436.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33509399
ABSTRACT
This is an update of the previous 2018 systematic review and meta-analysis of vitamin and mineral supplementation on cardiovascular disease outcomes and all-cause mortality. New randomized controlled trials and meta-analyses were identified by searching the Cochrane library, Medline, and Embase, and data were analyzed using random effects models and classified by the Grading of Recommendations Assessment Development and Evaluation approach. This updated review shows similar findings to the previous report for preventive benefits from both folic acid and B vitamins for stroke and has been graded with moderate quality. No effect was seen for the commonly used multivitamins, vitamin D, calcium, and vitamin C, and an increased risk was seen with niacin (with statin) for all-cause mortality. Conclusive evidence for the benefit of supplements across different dietary backgrounds, when the nutrient is sufficient, has not been demonstrated.

[36] *Uematsu M, Nakamura T, Horikoshi T et al.* **Echolucency of carotid plaque is useful for selecting high-risk patients with chronic coronary artery disease who benefit from intensive lipid-lowering therapy**. J Cardiol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33500186
ABSTRACT

BACKGROUND: Ultrasound assessment of the carotid artery provides prognostic information on coronary events. This study examined whether ultrasound assessments of plaque echolucency of the carotid artery are useful for identifying patients with coronary artery disease (CAD) who are at high risk but could benefit from lipid-lowering therapy for secondary prevention. METHODS: Ultrasound assessment of carotid plaque echolucency with integrated backscatter (IBS) analysis was performed in 393 chronic CAD patients with low-density lipoprotein cholesterol (LDL-C) levels <100 mg/dL on statin therapy. All patients were prospectively followed up for a maximum of 96 months or until the occurrence of one of the following coronary events: cardiac death, nonfatal myocardial infarction, or unstable angina pectoris requiring unplanned revascularization. RESULTS: During the follow-up period, 45 coronary events occurred. Patients were stratified by IBS (≤-16.3 or >-16.3 dB, median value) and LDL-C level (<70 or 70-99 mg/dL). Multivariate Cox proportional hazards analysis showed that patients with lower IBS and LDL-C 70-99 mg/dL had significantly higher probabilities of coronary events compared with those with higher IBS and LDL-C <70 mg/dL, after adjustment for a baseline model of risk factors (hazard ratio 5.15; 95% confidence interval 1.21-22.0, $p = 0.03$). In contrast, patients with lower IBS and LDL-C <70 mg/dL had an improved prognosis comparable with those with higher IBS. Addition of LDL-C levels to the baseline model of risk factors improved net reclassification improvement (NRI) and integrated discrimination improvement (IDI) in patients with lower IBS (NRI, 0.44, $p = 0.04$; and IDI, 0.035, $p < 0.01$), but not in those with higher IBS. CONCLUSIONS: Evaluation of echolucency of the carotid artery was useful for selecting CAD patients at high risk of secondary coronary events but who could benefit from lipid-lowering therapy.

[37] *Tmoyan NA, Afanasieva OI, Ezhov MV et al.* **Lipoprotein(a), Immunity, and Inflammation in Polyvascular Atherosclerotic Disease**. Journal of cardiovascular development and disease 2021; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33513851

ABSTRACT

BACKGROUND AND AIMS: lipoprotein(a) (Lp(a)) is a genetically determined risk factor for coronary artery disease and its complications, although data on the association with other vascular beds and the severity of atherosclerosis is limited. The aim of this study was to evaluate the association of atherosclerosis of various vascular beds with Lp(a), as well as its autoantibodies and generalized inflammatory markers. MATERIAL AND METHODS: this study included 1288 adult patients with clinical and imaging examination of three vascular beds (coronary, carotid, and lower limb arteries). Patients were categorized according to the number of affected vascular beds (with at least one atherosclerotic stenosis ≥50%): 0 (n = 339), 1 (n = 470), 2 (n = 315), 3 (n = 164). We assessed blood cell count, lipid profile, C-reactive protein, circulating immune complexes, Lp(a), and its autoantibodies. RESULTS: the number of affected vascular beds was associated with an increasing level of Lp(a) and a lower level of IgM autoantibodies to Lp(a). Hyperlipoproteinemia(a) (Lp(a) ≥ 30 mg/dL) was detected more frequently in patients with atherosclerosis. In logistic regression analysis adjusted for age, sex, hypertension, type 2 diabetes, and smoking, an elevated Lp(a) level was independently associated with stenotic atherosclerosis and lesion severity. There was a positive association of the number of affected vascular beds with C-reactive protein ($r = 0.21$, $p < 0.01$) and a

negative association with circulating immune complexes ($r = -0.29$, $p < 0.01$). The neutrophil-to-lymphocyte ratio was significantly higher and the lymphocyte-to-monocyte ratio was significantly lower in patients with atherosclerosis compared to the controls ($p < 0.01$). CONCLUSION: Lp(a), C-reactive protein, circulating immune complexes, and neutrophil-to-lymphocyte ratio are associated with the stenotic atherosclerosis of different vascular beds. Lp(a) levels increase and IgM autoantibodies to Lp(a) decrease with the number of affected vascular beds.

[38] *Imran TF, Kim E, Buring JE et al.* **Nut consumption, risk of cardiovascular mortality, and potential mediating mechanisms: The Women's Health Study**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33500188
ABSTRACT
BACKGROUND: The link between nut consumption and cardiovascular (CV) mortality remains unclear. OBJECTIVE: to examine whether nut consumption is associated with CV mortality and estimate the proportion of reduced risk of CV mortality explained by intermediate factors. METHODS: We studied 39,167 women from the Women's Health Study; 28,034 provided blood samples. Nut consumption was self-reported at baseline and at follow-up using a food frequency questionnaire. Our primary outcome was cardiovascular death, which was ascertained via medical records, confirmed with the national death index and death certificates. RESULTS: During a mean follow-up of 19 years, 959 CV deaths occurred. In a multivariable Cox regression model adjusting for age, body mass index, smoking, alcohol use, physical activity, postmenopausal status, marital status, family history of premature myocardial infarction and the alternate healthy eating index score, hazard ratios for CV mortality were 0.93 (0.76-1.14) for nut consumption of 1-3 times/month, 0.84 (0.69-1.01) for nut intake of 1 time/week, and 0.73 (0.61-0.87) for nut consumption of ≥2 times/week when compared to women who did not consume nuts ($p = 0.0004$). LDL and total cholesterol accounted for about 19%, HbA1c 18% and all mediating factors together accounted for about 6.6% of the lower risk of CV mortality for those who consumed nuts ≥2 times/week. For the secondary outcome of CV events, although the effect was noted to be in the same direction with increasing nut consumption associated with lower risk of CV events, it was not statistically significant ($p = 0.07$). CONCLUSION: This study suggests that nut consumption is inversely associated with cardiovascular mortality in women. Lipids, inflammatory markers and glucose metabolism account for a modest proportion of the lowered CV mortality observed with nut consumption, assuming a causal nut-CV mortality association.

[39] *Nkeh-Chungag BN, Goswami N, Engwa GA et al.* **Relationship between Endothelial Function, Antiretroviral Treatment and Cardiovascular Risk Factors in HIV Patients of African Descent in South Africa: A Cross-Sectional Study**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33498530
ABSTRACT
Limited information on the effect of antiretroviral treatment (ART) on vascular function in South Africans of African descent living with human immunodeficiency virus (HIV) is available. The

relationship between ART, vascular function and cardiovascular risk factors in South Africans of African ancestry with HIV was therefore studied. This cross-sectional study recruited 146 HIV-positive individuals on ART (HIV(+)ART(+)), 163 HIV-positive individuals not on ART (HIV(+)ART(-)) and 171 individuals without HIV (HIV(-)) in Mthatha, Eastern Cape Province of South Africa. Flow-mediated dilation (FMD) test was performed to assess endothelial function. Anthropometry and blood pressure parameters were measured. Lipid profile, glycaemic indices, serum creatinine as well as CD4 count and viral load were assayed in blood. Urinary albumin to creatinine ratio (ACR) was determined as a marker of cardiovascular risk. Obesity and albuminuria were positively associated with HIV, and HIV(+)ART(+) participants had significantly higher HDL cholesterol. Dyslipidaemia markers were significantly higher in hypertensive HIV(+)ART(+) participants compared with the controls (HIV(+)ART(-) and HIV(-) participants). FMD was not different between HIV(+)ART(+) participants and the controls. Moreover, HIV(+)ART(+) participants with higher FMD showed lower total cholesterol and LDL cholesterol comparable to that of HIV(-) and HIV(+)ART(-) participants. A positive relationship between FMD and CD4 count was observed in HIV(+)ART(+) participants. In conclusion, antiretroviral treatment was associated with cardiovascular risk factors, particularly dyslipidaemia, in hypertensive South Africans of African ancestry with HIV. Although, ART was not associated with endothelial dysfunction, flow-mediated dilatation was positively associated with CD4 count in HIV-positive participants on ART.

[40] *Wang N, Liu Q, Liu H et al.* **Association of Apolipoprotein E Polymorphisms and Risks of Ischemic Stroke in Chinese Patients with Type 2 Diabetes Mellitus**. Journal of diabetes research 2021; 2021:8816996.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33490286

ABSTRACT

BACKGROUND: The apolipoprotein E (APOE) gene polymorphisms have been intensively studied in patients with type 2 diabetes mellitus (T2DM) and ischemic stroke (IS) in recent years. However, it is unclear whether APOE gene polymorphisms are correlated with increased risk for developing IS in T2DM patients. Thus, this study was designed to examine the association between APOE gene polymorphisms and risks of IS in Chinese patients with T2DM. METHODS: This case-control study enrolled 243 subjects with T2DM as controls, and 210 subjects with T2DM complicated with IS as case patients. The genotypes were determined using real-time PCR while HbA1c and lipid levels were detected using commercially available kits. RESULTS: The systolic blood pressure (SBP), diastolic blood pressure (DBP), and the proportion of patients with a history of hypertension were higher in the case patients than that in the controls. We confirmed that the ε2/ε3 genotype, as well as SBP and history of hypertension, was the independent risk factor for developing IS in T2DM patients. CONCLUSIONS: We conclude that the ε2/ε3 genotype might contribute to the increased risk for developing IS in Chinese patients with T2DM.

[41] *Dusuel A, Deckert V, Pais de Barros JP et al.* **Human cholesteryl ester transfer protein lacks lipopolysaccharide transfer activity, but worsens inflammation and sepsis outcomes in mice**. Journal of lipid research 2020; 62:100011.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33500240

ABSTRACT
Bacterial lipopolysaccharides (LPSs or endotoxins) can bind most proteins of the lipid transfer/LPS-binding protein (LT/LBP) family in host organisms. The LPS-bound LT/LBP proteins then trigger either an LPS-induced proinflammatory cascade or LPS binding to lipoproteins that are involved in endotoxin inactivation and detoxification. Cholesteryl ester transfer protein (CETP) is an LT/LBP member, but its impact on LPS metabolism and sepsis outcome is unclear. Here, we performed fluorescent LPS transfer assays to assess the ability of CETP to bind and transfer LPS. The effects of intravenous (iv) infusion of purified LPS or polymicrobial infection (cecal ligation and puncture [CLP]) were compared in transgenic mice expressing human CETP and wild-type mice naturally having no CETP activity. CETP displayed no LPS transfer activity in vitro, but it tended to reduce biliary excretion of LPS in vivo. The CETP expression in mice was associated with significantly lower basal plasma lipid levels and with higher mortality rates in both models of endotoxemia and sepsis. Furthermore, CETPTg plasma modified cytokine production of macrophages in vitro. In conclusion, despite having no direct LPS binding and transfer property, human CETP worsens sepsis outcomes in mice by altering the protective effects of plasma lipoproteins against endotoxemia, inflammation, and infection.

[42] *Ference BA, Kastelein JJP, Catapano AL*. **Update on Lipids and Lipoproteins-Reply**. Jama 2021; 325:400-401.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33496768
ABSTRACT

[43] *Jialal I, Devaraj S*. **Update on Lipids and Lipoproteins**. Jama 2021; 325:400.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33496766
ABSTRACT

[44] *Armstrong MK, Fraser BJ, Hartiala O et al.* **Association of Non-High-Density Lipoprotein Cholesterol Measured in Adolescence, Young Adulthood, and Mid-Adulthood With Coronary Artery Calcification Measured in Mid-Adulthood**. JAMA cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33502454
ABSTRACT
IMPORTANCE: Elevated non-high-density lipoprotein cholesterol (non-HDL-C) is associated with the presence of coronary artery calcification (CAC), a marker of heart disease in adulthood. However, the relative importance of non-HDL-C levels at specific life stages for CAC remains unclear. OBJECTIVE: To identify the relative association of non-HDL-C measured at distinct life stages (adolescence, young adulthood, mid-adulthood) with the presence of CAC measured in mid-adulthood. DESIGN, SETTING, AND PARTICIPANTS: The Cardiovascular Risk in Young Finns Study is a population-based prospective cohort study that started in 1980 with follow-up over 28 years. Participants from 3 population centers (Kuopio, Tampere, and Turku in Finland) represent a convenience sample drawn from the 3 oldest cohorts at baseline (aged 12-18 years in 1980). Data were collected from September 1980 to August 2008. Analysis began February 2020. EXPOSURES: Non-HDL-C levels were

measured at 3 life stages including adolescence (aged 12-18 years), young adulthood (aged 21-30 years), and mid-adulthood (aged 33-45 years). MAIN OUTCOMES AND MEASURES: In 2008, CAC was determined from computed tomography and dichotomized as 0 (no CAC, Agatston score = 0) and 1 (presence of CAC, Agatston score ≥1) for analysis. Using a bayesian relevant life course exposure model, the relative association was determined between non-HDL-C at each life stage and the presence of CAC in mid-adulthood. RESULTS: Of 589 participants, 327 (56%) were female. In a model adjusted for year of birth, sex, body mass index, systolic blood pressure, blood glucose level, smoking status, lipid-lowering and antihypertensive medication use, and family history of heart disease, cumulative exposure to non-HDL-C across all life stages was associated with CAC (odds ratio [OR], 1.50; 95% credible interval [CrI], 1.14-1.92). At each life stage, non-HDL-C was associated with CAC and exposure to non-HDL-C during adolescence had the strongest association (adolescence: OR, 1.16; 95% CrI, 1.01-1.46; young adulthood: OR, 1.14; 95% CrI, 1.01-1.43; mid-adulthood: OR, 1.12; 95% CrI, 1.01-1.34). CONCLUSIONS AND RELEVANCE: These data suggest that elevated non-HDL-C levels at all life stages are associated with coronary atherosclerosis in mid-adulthood. However, adolescent non-HDL-C levels showed the strongest association with the presence of CAC in mid-adulthood, and greater awareness of the importance of elevated non-HDL-C in adolescence is needed.

[45] *Georgakis MK, Harshfield EL, Malik R et al.* **Diabetes Mellitus, Glycemic Traits, and Cerebrovascular Disease: A Mendelian Randomization Study**. Neurology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33495378

ABSTRACT

OBJECTIVE: We employed Mendelian randomization (MR) to explore the effects of genetic predisposition to type 2 diabetes (T2D), hyperglycemia, insulin resistance, and β-cell dysfunction on risk of stroke subtypes and related cerebrovascular phenotypes. METHODS: We selected instruments for genetic predisposition to T2D (74,124 cases, 824,006 controls), HbA1c levels (n=421,923), fasting glucose levels (n=133,010), insulin resistance (n=108,557), and β-cell dysfunction (n=16,378) based on published genome-wide association studies. Applying two-sample MR, we examined associations with ischemic stroke (60,341 cases, 454,450 controls), intracerebral hemorrhage (1,545 cases, 1,481 controls), and ischemic stroke subtypes (large artery, cardioembolic, small vessel stroke), as well as with related phenotypes (carotid atherosclerosis, imaging markers of cerebral white matter integrity, and brain atrophy). RESULTS: Genetic predisposition to T2D and higher HbA1c levels were associated with higher risk of any ischemic stroke, large artery stroke, and small vessel stroke. Similar associations were also noted for carotid atherosclerotic plaque, fractional anisotropy, a white matter disease marker, and markers of brain atrophy. We further found associations of genetic predisposition to insulin resistance with large artery and small vessel stroke, whereas predisposition to β-cell dysfunction was associated with small vessel stroke, intracerebral hemorrhage, lower grey matter volume, and total brain volume. CONCLUSIONS: This study supports causal effects of T2D and hyperglycemia on large artery and small vessel stroke. We show associations of genetically predicted insulin resistance and β-cell dysfunction with large artery and small vessel stroke that might have implications for anti-diabetic treatments targeting these mechanisms. CLASSIFICATION OF EVIDENCE: This study provides Class II

evidence that genetic predisposition to T2D and higher HbA1c levels are associated with a higher risk of large artery and small vessel ischemic stroke.

[46] *Wu YR, Li L, Sun XC et al.* **Diallyl disulfide improves lipid metabolism by inhibiting PCSK9 expression and increasing LDL uptake via PI3K/Akt-SREBP2 pathway in HepG2 cells**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021; 31:322-332.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33500108

ABSTRACT

BACKGROUND AND AIM: Diallyl disulfide (DADS), a volatile sulfide extracted from garlic, has been suggested as a chemical of anti-atherosclerotic drugs, while its molecular mechanism for this benefit has not fully been understood. The aim of the present study was to investigate the effects of DADS on lipid metabolism and its potential mechanisms in HepG2 cells induced by lipopolysaccharides (LPS). METHODS AND RESULTS: HepG2 cells were treated with LPS with or without different concentrations of DADS (0, 20, 40, 80, 160 μg/ml) for 24 h. The cell activity was detected by CCK8, and Dil-LDL uptake assay was used to examine the LDL uptake. Real-time PCR and Western blot were used to detect the expression of LDLR, PCSK9 SREBP2 and HMGCR. In addition, we examined the effect of the combination of DADS with atorvastatin on PCSK9 expression. The results showed that LPS significantly increased PCSK9 and SREBP2 expressions in a dose-dependent manner in HepG2 cells. DADS attenuated PCSK9, SREBP2 and HMGCR expressions and up-regulated the expression of LDLR. Moreover, DADS reversed the expressions of PCSK9, SREBP2, HMGCR and LDLR induced by LPS and DADS could promote the LDL uptake in HepG2 cells. Furthermore, DADS decreased the expression of PCSK9 by activating the PI3K/Akt-SREBP2 signal pathway. Notably, DADS could reduce PCSK9 expression induced by atorvastatin in HepG2 cells. CONCLUSION: DADS could significantly attenuated PCSK9 expression in a dose-dependent manner induced by LPS and increased the LDLR expression in HepG2 cells, which was associated with the activation of PI3K/Akt-SREBP2 signaling pathway.

[47] *Przulj D, Ladmore D, Smith KM et al.* **Time restricted eating as a weight loss intervention in adults with obesity**. PloS one 2021; 16:e0246186.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33508009

ABSTRACT

OBJECTIVES: Time-restricted eating (TRE) is a weight management approach in which food is consumed only within a specific period each day. The simplicity of this approach is appealing, but its efficacy is not known. The aim of this pilot cohort study was to assess adherence to TRE and its effects on weight and lipid profile. METHODS: Fifty participants with obesity attempted to follow TRE for 12 weeks. Surveys were conducted weekly over the phone to assess treatment adherence and ratings; and at 6 and 12 weeks, participants attended the clinic to be weighed, have their blood pressure taken and provide a blood sample for lipid profile. Treatment results were compared with data from previous comparable cohorts using other weight management methods. RESULTS: Mean age of the participants was 50 (SD = 12.0), mean weight 97kg (SD = 17.1), mean BMI = 35 (SD = 4.0) and most were female (74%). At weeks 6 and 12, 64% and 58% of participants continued to practice TRE on at least five days/week. Using the 'last observation carried forward' imputation, mean (SD) weight loss was

2.0 (1.7) kg and 2.6 (2.6) kg at 6 and 12 weeks. Among participants who provided follow-up data, those who adhered to the intervention for at least five days/week recorded greater weight loss than those with lower adherence (week 6: 2.5 (1.7) vs 1.0 (1.3), p = 0.003; week 12: 3.5 (2.7) vs 1.3 (2.0), p = 0.001). A total of 26% of the sample lost at least 5% of their body weight at 12 weeks. The intervention had no effect on blood pressure or lipid profile. CONCLUSIONS: TRE results were modest, but at least on par with those achieved with more complex interventions, and weight loss did not decline at 12 weeks. A formal trial of the intervention is warranted.

[48] *Sanda GM, Stancu CS, Deleanu M et al.* **Aggregated LDL turn human macrophages into foam cells and induce mitochondrial dysfunction without triggering oxidative or endoplasmic reticulum stress**. PloS one 2021; 16:e0245797.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33493198
ABSTRACT
Uptake of modified lipoproteins by macrophages turns them into foam cells, the hallmark of the atherosclerotic plaque. The initiation and progression of atherosclerosis have been associated with mitochondrial dysfunction. It is known that aggregated low-density lipoproteins (agLDL) induce massive cholesterol accumulation in macrophages in contrast with native LDL (nLDL) and oxidized LDL (oxLDL). In the present study we aimed to assess the effect of agLDL on the mitochondria and ER function in macrophage-derived foam cells, in an attempt to estimate the potential of these cells, known constituents of early fatty streaks, to generate atheroma in the absence of oxidative stress. Results show that agLDL induce excessive accumulation of free (FC) and esterified cholesterol in THP-1 macrophages and determine mitochondrial dysfunction expressed as decreased mitochondrial membrane potential and diminished intracellular ATP levels, without generating mitochondrial reactive oxygen species (ROS) production. AgLDL did not stimulate intracellular ROS (superoxide anion or hydrogen peroxide) production, and did not trigger endoplasmic reticulum stress (ERS) or apoptosis. In contrast to agLDL, oxLDL did not modify FC levels, but stimulated the accumulation of 7-ketocholesterol in the cells, generating oxidative stress which is associated with an increased mitochondrial dysfunction, ERS and apoptosis. Taken together, our results reveal that agLDL induce foam cells formation and mild mitochondrial dysfunction in human macrophages without triggering oxidative or ERS. These data could partially explain the early formation of fatty streaks in the intima of human arteries by interaction of monocyte-derived macrophages with non-oxidatively aggregated LDL generating foam cells, which cannot evolve into atherosclerotic plaques in the absence of the oxidative stress.

[49] *Kallio P, Pahkala K, Heinonen OJ et al.* **Physical inactivity from youth to adulthood and adult cardiometabolic risk profile**. Prev Med 2021:106433.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33497685
ABSTRACT
Adults with a low physical activity (PA) level are at increased risk for cardiometabolic diseases, but little is known on the association between physical inactivity since youth and cardiometabolic health in adulthood. We investigated the association of persistent physical inactivity from youth to adulthood with adult cardiometabolic risk factors. Data were drawn from

the ongoing Cardiovascular Risk in Young Finns Study with seven follow-ups between 1980 and 2011 (baseline age 3-18 years, n = 1961). Physical activity data from a standardized questionnaire was expressed as a PA-index. Using the PA-index, four groups were formed: 1)persistently physically inactive (n = 246), 2)decreasingly active (n = 305), 3)increasingly active (n = 328), and 4)persistently active individuals (n = 1082). Adulthood cardiometabolic risk indicators included waist circumference, body mass index (BMI), blood pressure, and fasting lipids, insulin, and glucose. Clustered cardiometabolic risk was defined using established criteria for metabolic syndrome. Persistently physically inactive group was used as a reference. Compared to the persistently physically inactive group, those who were persistently active had lower risk for adult clustered cardiometabolic risk (RR = 0.67;CI95% = 0.53-0.84; Harmonized criteria), obesity (BMI > 30 kg/m(2), RR = 0.76;CI95% = 0.59-0.98), high waist circumference (RR = 0.82;CI95% = 0.69-0.98), and high triglyceride (RR = 0.60;CI95% = 0.47-0.75), insulin (RR = 0.58;CI95% = 0.46-0.74) and glucose (RR = 0.77;CI95% = 0.62-0.96) concentrations as well as low high-density lipoprotein cholesterol (HDLC) concentration (RR = 0.78;CI95% = 0.66-0.93). Comparable results were found when persistently physically inactive individuals were compared with those who increased PA. The results remained essentially similar after adjustment for education, diet, smoking, and BMI. Persistently physically inactive lifestyle since youth is associated with an unfavorable cardiometabolic risk profile in adulthood. Importantly, even minor increase in PA lowers the cardiometabolic risk.

[50] *Mupparapu M, Nath S*. **Calcified carotid artery atheroma and stroke risk assessment. Use of Doppler ultrasonography as a secondary marker: a meta-analysis**. Quintessence Int 2021; 0:0.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33491393

ABSTRACT

Objective: Calcified carotid artery atheroma (CCAA) detected by panoramic radiographs has been suggested as an accurate biomarker for cerebrovascular accidents (CVAs). However, there has not been agreement on the relationship between CCAA and risk for stroke or other CVA. Method and materials: The question asked was, "Are patients with CCAA detected on panoramic radiographs more likely to get a stroke or CVA in the future compared to those who do not have CCAA and, further, would Doppler ultrasonography of the neck obtained secondary to panoramic radiography in suspected individuals add value to this association with stroke or CVA?" This meta-analysis was conducted by searching PubMed, Ovid Medline, Dentistry & Oral Sciences Source, CINAHL, Web of Science, Google Scholar, and ClinicalTrials.gov. Six studies that met the inclusion criteria were included in the final analysis; three used panoramic radiography and the rest used panoramic radiography and ultrasonography. Multiple random effect meta-analyses were conducted using RevMan 5.2 software. Conclusion: Evidence from this meta-analysis shows that although detection of CCAA via panoramic radiography to predict risk for stroke may be comparable to Doppler ultrasonography, risk prediction is somewhat more significant when diagnostic confirmation is made using Doppler ultrasonography than panoramic radiography alone. Clinical implications: Because stroke risk assessment is complicated and comprises many additional systemic factors beyond calcification of the carotid artery, CVA prediction is more reliable when Doppler ultrasonography is used after panoramic radiography. Managing hypertension, diabetes, and

smoking habit are far more important in risk management of patients with CCAA detection on panoramic radiography.

[51] *Strauss M, Foshag P, Jehn U et al.* **Higher cardiorespiratory fitness is strongly associated with lower cardiovascular risk factors in firefighters: a cross-sectional study in a German fire brigade**. Scientific reports 2021; 11:2445.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33510237
ABSTRACT
Previous studies have shown significant cardiovascular risks in firefighters and that they suffer from cardiovascular events, especially on duty. Otherwise, adequate cardiorespiratory fitness is considered to have a protective effect in reducing cardiovascular complications. Therefore, the study aimed to evaluate the association between cardiorespiratory fitness and cardiovascular risks factors in firefighters. We enrolled ninety-seven male German firefighters in this cross-sectional study of cardiorespiratory fitness and cardiovascular risk factors. We used spiroergometry testing to estimate oxygen consumption to determine cardiorespiratory fitness and to calculate metabolic equivalents. We evaluated cardiovascular risk factors included nicotine consumption, lipid profiles, body composition, resting blood pressure, and heart rate. We evaluated cardiovascular risk factors included nicotine consumption, lipid profiles, body composition, resting blood pressure and heart rate. The comparison of association between cardiorespiratory fitness and cardiovascular risk factors was performed by using $\chi(2)$-test, analysis of variance, general linear regression with/without adjustment for age and body mass index (BMI). This study demonstrated a strong association between lower cardiovascular risk factors and higher cardiorespiratory fitness. There were significantly lower values for BMI, waist circumference, body fat percentage and resting systolic blood pressure, triglycerides, and total cholesterol (all $p<0.0443$, age-adjusted) with increased cardiorespiratory fitness. Only 19.6% ($n=19$) of the examined firefighters were classified as "fit and not obese", 48.4% ($n=47$) were "low fit and not obese" and 30.9% ($n=30$) were "low fit and obese". The results clarify that increasing cardiorespiratory fitness is a fundamental point for the reduction and prevention of cardiovascular complications in firefighters. It could be demonstrated, especially for central risk factors, particularly BMI, waist circumference, sytolic resting blood pressure and triglyceride values. Therefore, firefighters should be motivated to increase their cardiorespiratory fitness for the beneficial effect of decreasing cardiovascular risk profile.

[52] *Hsu BG, Tsai JP*. **Vascular calcification of chronic kidney disease: A brief review**. Tzu Chi Med J 2021; 33:34-41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33505876
ABSTRACT
Vascular calcification (VC) is highly prevalent among patients with chronic kidney disease (CKD). There is growing evidence that there is more underlying this condition than the histological presentation of atherosclerotic plaque and arteriosclerosis and that the risk of cardiovascular disease in the context of CKD might be explained by the presence of VC. While VC has been observed in the absence of overt abnormal mineral metabolism, this association is coupled to abnormal homeostasis of minerals in patients with CKD, due to

hyperphosphatemia and hypercalcemia. Furthermore, recent studies have shown that the differentiation of vascular smooth muscle cells into an osteogenic phenotype is highly regulated by pro-calcifying and anti-calcifying factors. There are several imaging modalities currently used in clinical practice to evaluate the extent and severity of VC; each has different advantages and limitations. Although there is no universally accepted method for the treatment of VC, there is growing evidence of the beneficial effects of medical therapy for the condition. This study discusses the mechanism underlying VC, imaging modalities used for evaluation of the condition, and possible treatments.

[53] *Park JK, Jung WB, Yoon JH*. **Distribution Pattern of Atherosclerosis in the Abdomen and Lower Extremities and Its Association with Clinical and Hematological Factors**. Vascular health and risk management 2021; 17:13-21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33488084
ABSTRACT
PURPOSE: Abdominal arteries differ from the arteries located at the extremities in histological composition and clinical features. This study investigated the distributional pattern of atherosclerosis in arteries of the abdomen and lower extremities and its association with clinical and hematologic factors. PATIENTS AND METHODS: This retrospective study included 227 patients with atherosclerosis who underwent computed tomography angiography (CTA) of the abdomen and lower extremities. The distributional pattern of atherosclerosis was categorized into type 1 (suprainguinal elastic), type 2 (infrainguinal muscular), and type 3 (both arterial involvement). Chi-square tests, Mann-Whitney U-tests, and logistic regression analysis were used to investigate the data. RESULTS: Of the 227 patients, 132 (58%) had type 1 and 95 (42%) had type 3 atherosclerosis. None had type 2. Older age, heavier smoking, and higher levels of HbA1c and homocysteine were the significant risk factors for type 3 atherosclerosis (odds ratio: 1.076, 1.023, 1.426, and 1.130, respectively). Patients with type 3 showed significantly lower right and left ankle and toe brachial indices compared to type 1 (P: 0.029, 0.023, 0.003, and <0.001, respectively). CONCLUSION: In arteries of the abdomen and lower extremities, atherosclerosis may occur initially at suprainguinal elastic arteries. In addition, the significant risk factors for type 3 atherosclerosis may contribute to the development of atherosclerosis at infrainguinal muscular arteries and deteriorate the peripheral arterial circulation. Therefore, if atherosclerotic lesions are found at the suprainguinal elastic arteries on CTA, to prevent atherosclerosis at infrainguinal muscular arteries and subsequent peripheral arterial ischemic disease, cessation of smoking and control of blood glucose and homocysteine may be recommended, especially in elderly patients.

[54] *Wang SS, Yang SS, Jia WP et al.* **[Distribution characteristics of blood lipid profile in Hainan centenarians]**. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi 2021; 42:80-87.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33503701
ABSTRACT
Objective: To explore the prevalence of lipid profile and the influencing factors of dyslipidemia in centenarians in Hainan province, and provide basic data for the study of the lipid profile in centenarians. Methods: The data of this study were from the baseline data of China Hainan

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Centenarian Cohort Study from June 2014 to December 2016. A total of 1 002 centenarians were recruited. According to the guidelines for the prevention and treatment of dyslipidemia in Chinese adults in 2016, the prevalence of lipid profile were described and the prevalence of dyslipidemia with different clinical classifications were compared, and the main influencing factors were analyzed. Results: The median levels of TC, TG, LDL-C and HDL-C were 4.60 mmol/L, 1.05 mmol/L, 2.77 mmol/L and 1.41 mmol/L, respectively, in centenarians in Hainan. Blood lipid profile level was higher in females than in males. With the increase of BMI, TC, TG and LDL-C increased significantly, while HDL-C decreased significantly. The total prevalence of dyslipidemia was 19.1%. Smoking, BMI and area distribution were the main influencing factors of dyslipidemia. Conclusion: The prevalence of dyslipidemia in centenarians in Hainan was at a low level compared with other countries, and the blood lipid profile level was higher in females than in males.